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(71) Applicant *(for all designated States except US)*: **DSM IP ASSETS B.V.** [NL/NL]; Het Overloon 1, NL-6411 TE Heerlen (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RAEDERSTORFF, Daniel** [FR/FR]; 36c rue Bellevue, F-68350 Brunstatt (FR). **TEIXEIRA, Sandra, Renata** [PT/CH]; Gempenstrasse 46, CH-4053 Basel (CH). **WEBER, Peter** [DE/DE]; Im Grundacker 10, 79429 Malsburg-Marzell (DE).

(74) Agent: **MUELLER, Ingrid**; Roche Vitamins Ltd., Patent Department (VMD), Wurmisweg 576, CH-4303 Kaiseraugst (CH).

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(54) Title: NOVEL NUTRACEUTICAL COMPOSITIONS COMPRISING EPIGALLOCATECHIN GALLATE

(57) Abstract: The invention relates to nutraceutical compositions comprising at least two ingredients from the groups of EGCG, pantethine or a metabolite thereof, phytanic acid, lipoic acid, policosanol and coenzyme Q-10 and their use in the treatment or prevention of diabetes or obesity.

Novel nutraceutical compositions comprising epigallocatechin gallate

The present invention relates to novel nutraceutical compositions comprising at least two components selected from EGCG, pantethine or a metabolite thereof, phytanic acid, lipoic acid, policosanol and coenzyme Q-10 as the active ingredients for the treatment or prevention of diabetes mellitus, or other conditions associated with impaired glucose tolerance such as syndrome X and obesity. In another aspect the present invention relates to the use of such compositions as a nutritional supplement for the said treatment or prevention, e.g., as an additive to a multi-vitamin preparations comprising vitamins and minerals which are essential for the maintenance of normal metabolic function but are not synthesized in the body. In still another aspect, the invention relates to a method for the treatment of both type 1 and 2 diabetes, and for the prevention of type 2 diabetes in those individuals with pre-diabetes, or impaired glucose tolerance (IGT) or obesity which comprises administering to a subject in need of such treatment at least two components selected from EGCG, pantethine or a metabolite thereof, phytanic acid, lipoic acid, policosanol and coenzyme Q-10.

The compositions of the present invention are particularly intended for the treatment of both type 1 and 2 diabetes, and for the prevention of type 2 diabetes in those individuals with pre-diabetes, or impaired glucose tolerance (IGT), or obesity.

The compositions comprising a combination of active ingredients, i.e., at least two components selected from EGCG, pantethine or a metabolite thereof, phytanic acid, lipoic acid, policosanol and coenzyme Q-10 have different mechanism of action on glucose metabolism and insulin sensitivity thus providing additive and/or synergetic effects in the treatment of diabetes.

The term nutraceutical as used herein denotes a usefulness in both the nutritional and pharmaceutical field of application. Thus, the novel nutraceutical compositions can find use as supplement to food and beverages, and as pharmaceutical formulations for enteral or parenteral application which may be solid formulations such as capsules or tablets, or liquid formulations, such as solutions or suspensions. As will be evident from the foregoing, the term nutraceutical composition also comprises food and beverages containing at least two components selected from EGCG, pantethine or a metabolite

thereof, phytanic acid, lipoic acid, policosanol and coenzyme Q-10, as well as supplement compositions containing the aforesaid active ingredients.

Diabetes is a widespread chronic disease that hitherto has no cure. The incidence and prevalence of diabetes is increasing exponentially and it is among the most common metabolic disorder in developed and developing countries. Diabetes mellitus is a complex disease derived from multiple causative factors and characterized by impaired carbohydrate, protein and fat metabolism associated with a deficiency in insulin secretion and or insulin resistance. This results in elevated fasting and postprandial serum glucose that leads to complications if left untreated. There are two major categories of the diseases, insulin-dependent diabetes mellitus (IDDM, type 1) and non-insulin-dependent diabetes mellitus (NIDDM, type 2).

Type 1 and type 2 diabetes are associated with hyperglycemia, hypercholesterolemia and hyperlipidemia. The insensitivity to insulin and absolute insulin deficiency in type 1 and 2 diabetes leads to a decrease in glucose utilization by the liver, muscle and the adipose tissue and to an increase in the blood glucose levels. Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for microvascular and macrovascular diseases, including nephropathy, neuropathy, retinopathy, hypertension, stroke, and heart disease. Recent evidence showed that tight glycemic control is a major factor in the prevention of these complications in both type 1 and type 2 diabetes mellitus. Therefore, optimal glycemic control by drugs or therapeutic regimens is an important approach for the treatment of diabetes.

Therapy of type 2 diabetes initially involves dietary and lifestyle changes, when these measures fail to maintain adequate glycemic control the patients are treated with oral hypoglycemic agents and/or exogenous insulin. The current oral pharmacological agents for the treatment of type 2 diabetes mellitus include those that potentiate insulin secretion (sulphonylurea agents), those that improve the action of insulin in the liver (biguanide agents), insulin sensitizing agents (thiazolidinediones) and agents which act to inhibit the uptake of glucose (α-glucosidase inhibitors). However, currently available agents generally fail to maintain adequate glycemic control in the long term due to progressive deterioration in hyperglycaemia, resulting from progressive loss of pancreatic cell function. The proportion of patients able to maintain target glycemic levels decreases markedly overtime necessitating the administration of additional/alternative pharmacological agents. Furthermore, the drugs may have unwanted side effects and are associated with high primary and secondary failure rates. Finally, the use of hypoglycemic drugs may be effective in controlling blood glucose levels, but may not prevent all the complications of

diabetes. Thus, current methods of treatment for all types of diabetes mellitus fail to achieve the ideals of normoglycemia and the prevention of diabetic complications.

Therefore, although the therapies of choice in the treatment of type 1 and type 2 diabetes are based essentially on the administration of insulin and of oral hypoglycemic drugs, there is a need for a safe and effective nutritional supplement with minimal side effects for the treatment and prevention of diabetes. Many patients are interested in alternative therapies which could minimize the side effects associated with high-dose of drugs and yield additive clinical benefits. Patients with diabetes have a special interest in treatment considered as "natural" with mild anti-diabetic effects and without major side effects, which can be used as adjuvant treatment. Type 2 diabetes is a progressive and chronic disease, which usually is not recognized until significant damage has occurred to the pancreatic cells responsible for producing insulin. Therefore, there is also an increasing interest in the development of a dietary supplement that may be used to prevent the development of diabetes in people at risk especially in elderly who are at high risk for developing diabetes. Furthermore, type 2 is a complicated disease resulting from coexisting defects at multiple organ sites: resistance to insulin action in muscle and adipose tissues, defective pancreatic insulin secretion, unrestrained hepatic glucose production associated with lipid abnormalities and endothelial dysfunction. Therefore, given the multiple pathophysiological lesions in type 2 diabetes, combination therapy is an attractive approach to its management.

The use of combinations of EGCG, pantethine or a metabolite thereof, Coenzyme Q-10, phytanic acid, policosanol and/or lipoic acid which individually exert different mechanisms of action are effective in achieving and maintaining target blood glucose levels in diabetic patients.

The combinations of the active ingredients identified above have been conceived because of their different actions, to take advantage of additive/synergetic and multiorgan effects. Owing to distinct mechanism of action of the individual active ingredients the combinations not only improve glycemic control, but also result in lower drug dosing in some settings and minimize adverse effects. Because of their distinct mechanism and sites of action, the specific combinations of dietary supplements discussed above also take advantage of additive/synergetic effects to achieve a degree of glucose lowering greater than single agents can accomplish. Thus, although the therapies of choice in the therapeutic treatment of type 1 and type 2 diabetes is based essentially on the administration of insulin and of oral hypoglycemic drugs appropriate nutritional therapy is also of major importance for the successful treatment of diabetics.

The function of each of the active ingredients of the nutraceutical compositions of the present invention is described below:

EGCG: Epigallocatechin gallate (EGCG) is the major catechin found in green tea. In rats green tea catechins dose-dependently suppressed the increase in glucose and insulin levels in plasma after a starch or a sucrose rich meal. Combinations of EGCG and pantethine or phytanic acid according to the invention are especially useful for patients who have impaired glucose tolerance, older patients who develop an increase in postprandial glucose due to aging, and patients with undiagnosed diabetes.

Pantethine: In human studies oral administration of pantethine resulted in a progressive decrease in total cholesterol, triglycerides, low density lipoprotein (LDL) cholesterol and an increase in high density lipoprotein (HDL) cholesterol. Thus, resulting in a more favorable Chol/HDL ratio which reduces cardiovascular risk. Diabetes mellitus is associated with a 3- to 4-fold increase in risk of coronary artery disease. Type 2 diabetes mellitus adversely affects the plasma lipid profile, increasing levels of atherogenic lipids such as low density lipoproteins (LDL) and very low density lipoproteins (VLDL), but decreasing levels of high density lipoprotein (HDL), an antiatherogenic lipid. Atherosclerotic manifestations are not only common in individuals with diabetes but also result in significant long-term complications. Therefore, the oral supplementation with pantethine helps diabetes patients to normalize their lipid values reducing the risk of coronary heart disease and of thrombotic events. Instead of or in addition to panthethine, metabolites of pantethine such as cysteamine and pantothenic acid may find use in accordance with the invention.

Lipoic acid: Lipoic acid (1,2-dithiolane-3-pentaenoic acid) plays an essential role in mitochondrial-specific pathways that generate energy from glucose and may potentially influence the rate of glucose oxidation. Lipoic acid stimulates glucose transport in both muscle and adipose cells in culture. Moreover, administration of lipoic acid also raised basal and insulin-stimulated glucose uptake by skeletal muscles of glucose intolerant and non-insulin dependent diabetic animals. Furthermore, lipoic acid improves glucose disposal in patients with type 2 and may be incorporated in a nutraceutical composition of the present invention in order to prevent and/or treat the diabetic related complications and as agent with insulin sensitizing activity.

Phytanic acid: Phytanic acid (3, 7, 11, 15- tetramethylhexadecanoic acid) at concentrations ranging from about 10 to about100μM enhances uptake of glucose in rat primary hepatocytes. Compared to the specific PPAR-γ agonist such as ciglitazone, phytanic acid exerts only minor effects on the differentiation of pre-adipocyte cells into mature adipocytes. Therefore, intake of phytanic acid helps to improve insulin sensitivity and may act as a preventative measure against type 2 diabetes and Syndrome X through activation of PPARs and RXR.

Coenzyme Q-10: Coenzyme Q-10, (6-Decaprenyl-2,3-dimethoxy-5-methyl-1,4-benzoquinone) is a fat soluble quinone with a structure similar to vitamin K. The health beneficial effects of Coenzyme Q10 (CoQ10) have been associated with its two main biochemical functions. CoQ10 is an essential cofactor of the mitochondrial electron transport chain which, is coupled to synthesis of adenosine triphosphate (ATP). Therefore, it acts as a catalyst in the biochemical pathway that leads to cellular energy production. This bioenergic effect of CoQ10 is of particular importance in cells with high metabolic demands such as cardiac myocytes. Moreover, CoQ10 is an important antioxidant in both the mitochondria and lipid membranes. CoQ10 exerts a sparing effect on vitamin E and has membrane stabilizing properties. Several studies showed that LDL oxidation was reduced after CoQ10 supplementation. Thus CoQ10 may improve energy metabolism and protect against oxidative stress in diabetes and cardiovascular diseases.

Policosanol: Policosanol is a mixture of primary aliphatic alcohols isolated and purified from plant waxes, mainly sugar cane. The aliphatic alcohol of the mixture is a CH_3-$(CH_2)_n$-CH_2 OH alcohol with chain length varying from 18 to 40 carbon atoms. Typical aliphatic alcohols of the mixture are octacosanol, hexacosanol, heptacosanol, triacontanol and dotriacontanol. Policosanol has been shown to lower cholesterol in animal models, healthy volunteers, and patients with type II hypercholesterolemia. Therefore, it is useful in the dyslipidemia associated with type 2 diabetes mellitus.

A multi-vitamin and mineral supplement may be added to the nutraceutical compositions of the present invention to obtain an adequate amount of an essential nutrient missing in some diets. The multi-vitamin and mineral supplement may also be useful for disease prevention and protection against nutritional losses and deficiencies due to lifestyle patterns and common inadequate dietary patterns sometimes observed in diabetes. Moreover, oxidant stress has been implicated in the development of insulin resistance. Reactive oxygen species may impair insulin stimulated glucose uptake by disturbing the insulin receptor signaling cascade. The control of oxidant stress with antioxidants such as α-tocopherol (vitamin E) ascorbic acid (vitamin C) may be of value in the treatment of

diabetes. Therefore, the intake of multi-vitamin supplement may be added to the above mentioned active substances to maintain a good balanced nutrition.

In a preferred aspect of the invention, the nutraceutical composition of the present invention contains EGCG which suitably is present in the composition according to the invention in an amount to provide a daily dosage from about 0.3 mg per kg body weight to about 30 mg per kg body weight of the subject to which it is to be administered. A food or beverage suitably contains about 5 mg per serving to about 500 mg per serving of EGCG. If the nutraceutical composition is a pharmaceutical formulation such formulation may contain EGCG in an amount from about 10 mg to about 500 mg per dosage unit, e.g., per capsule or tablet, or from about 20 mg per daily dose to about 2000 mg per daily dose of a liquid formulation.

In another preferred aspect of the invention, the nutraceutical composition of the present invention further contains pantethine. The amount of pantethine in the composition may be such to provide a daily dosage from about 1 mg per kg body weight to about 50 mg per kg body weight of the subject to which it is to be administered. A food or beverage suitably contains about 20 mg per serving to about 800 mg per serving of pantethine. If the nutraceutical composition is a pharmaceutical formulation such formulation may contain pantethine in an amount from about 20 mg to about 1000 mg per dosage unit, e.g., per capsule or tablet, or from about 70 mg per daily dose to about 3500 mg per daily dose of a liquid formulation.

If phytanic acid is present in the nutraceutical composition according to the invention its amount may be such to provide a daily dosage from about 1 mg per kg body weight to about 100 mg per kg body weight of the subject to which it is to be administered. A food or beverage suitably contains about 20 mg per serving to about 2000 mg per serving of phytanic acid. If the nutraceutical composition is a pharmaceutical formulation such formulation may contain phytanic acid in an amount from about 30 mg to about 500 mg per dosage unit, e.g., per capsule or tablet, or from about 70 mg per daily dose to about 7000 mg per daily dose of a liquid formulation. Phytanic acid may also be used in the form of a biologically equivalent derivative thereof, such as an ester, e.g. the methyl or ethyl ester.

If lipoic acid is present in the nutraceutical composition according to the invention its amount may be such to provide a daily dosage from about 0.3 mg per kg body weight to about 30 mg per kg body weight of the subject to which it is to be administered. A food or beverage suitably contains about 5 mg per serving to about 500 mg per serving of lipoic acid. If the nutraceutical composition is a pharmaceutical formulation such formulation

may contain lipoic acid in an amount from about 5 mg to about 800 mg per dosage unit, e.g., per capsule or tablet, or from about 5 mg per daily dose to about 2000 mg per daily dose of a liquid formulation.

If Coenzyme Q-10 is present in the nutraceutical composition according to the invention its amount may be such to provide a daily dosage from about 0.01 mg per kg body weight to about 30 mg per kg body weight of the subject to which it is to be administered. A food or beverage suitably contains about 1 mg per serving to about 400 mg per serving of CoQ10. If the nutraceutical composition is a pharmaceutical formulation such formulation may contain CoQ10 in an amount from about 1 mg to about 500 mg per dosage unit, e.g., per capsule or tablet, or from about 1 mg per daily dose to about 2000 mg per daily dose of a liquid formulation.

If policosanol is present in the nutraceutical composition according to the invention its amount may be such to provide a daily dosage from about 0.002 mg per kg body weight to about 1.5 mg per kg body weight of the subject to which it is to be administered. A food or beverage suitably contains about 0.1 mg per serving to about 20 mg per serving of policosanol. If the nutraceutical composition is a pharmaceutical formulation such formulation may contain policosanol in an amount from about 0.1 mg to about 30 mg per dosage unit, e.g., per capsule or tablet, or from about 0.1 mg per daily dose to about 100 mg per daily dose of a liquid formulation.

Preferred nutraceutical compositions of the present invention comprise combinations of at least two components selected from EGCG, pantethine or a metabolite thereof, phytanic acid, lipoic acid and coenzyme Q-10, more particularly EGCG, panthetine, phytanic acid and Coenzyme Q-10, especially the combinations of

EGCG and pantethine;

EGCG and phytanic acid;

Pantethine and phytanic acid;

EGCG and Coenzyme Q-10;

EGCG, phytanic acid and Coenzyme Q-10;

EGCG, phytanic acid and pantethine; and

EGCG, phytanic acid, pantethine and Coenzyme Q-10.

Most preferred are the combinations of EGCG and pantethine or phytanic acid, and the combination of pantethine and phytanic acid.

Dosage ranges (for a 70 kg person)

EGCG: 20-2100 mg/day

Pantethine: 70-3500 mg/day

Phytanic acid: 70-7000 mg/day

Coenzyme Q-10: 1-2100 mg/day

Lipoic acid: 20-2100 mg/day

Policosanol: 0.15-100 mg/day

The following Examples illustrate the invention further.

A. Pharmaceutical compositions may be prepared by conventional formulation procedures using the ingredients specified below:

Example 1

Soft gelatin capsule

Soft gelatin capsules are prepared by conventional procedures using ingredients specified below:

Active ingredients: EGCG 300 mg Pantethine 100 mg

Other ingredients: glycerol, water, gelatine, vegetable oil

Example 2

Hard gelatin capsule

Hard gelatin capsules are prepared by conventional procedures using ingredients specified below:

Active ingredients: EGCG 150 mg Pantethine 100 mg

Other ingredients:

Fillers: lactose or cellulose or cellulose derivatives q.s

Lubricant: magnesium sterate if necessary (0.5%)

Example 3

Tablet

Tablets are prepared by conventional procedures using ingredients specified below:

Active ingredients: EGCG 100 mg, pantethine 50 mg

Other ingredients: microcrystalline cellulose, silicone dioxide (siO2), magnesium stearate, crosscarmellose sodium.

B. Food items may be prepared by conventional procedures using ingredients specified below:

Example 4

Soft Drink with 30% juice

Typical serving: 240 ml
Active ingredients:

EGCG and one or more additional components selected from pantethine, Coenzyme Q-10, phytanic acid and lipoic acid are incorporated in this food item

Pantethine: 20-800 mg/ per serving
EGCG: 5-500 mg/ per serving
Phytanic acid: 20-2000 mg/ per serving
Coenzyme Q-10: 1-400 mg /per serving
Lipoic acid: 5-500 mg/ per serving
Policosanol: 0.1-20 mg/ per serving

I. A Soft Drink Compound is prepared from the following ingredients :

Juice concentrates and water soluble flavours

	[g]
1.1 Orange concentrate	
60.3 °Brix, 5.15% acidity	657.99
Lemon concentrate	
43.5 °Brix, 32.7% acidity	95.96
Orange flavour, water soluble	13.43
Apricot flavour, water soluble	6.71
Water	26.46
1.2 Color	
β-Carotene 10% CWS	0.89

Water	67.65

1.3 Acid and Antioxidant

Ascorbic acid	4.11
Citric acid anhydrous	0.69
Water	43.18

1.4 Stabilizers

Pectin	0.20
Sodium benzoate	2.74
Water	65.60

1.5 Oil soluble flavours

Orange flavour, oil soluble	0.34
Orange oil distilled	0.34

1.6 Active ingredients

Active ingredients (this means the active ingredient mentioned above: EGCG and one or more of pantethine, Coenzyme Q-10, lipoic acid, policosanol and/or phytanic acid) in the concentrations mentioned above

Fruit juice concentrates and water soluble flavours are mixed without incorporation of air. The color is dissolved in deionized water. Ascorbic acid and citric acid is dissolved in water. Sodium benozoate is dissolved in water. The pectin is added unter stirring and dissolved while boiling. The solution is cooled down.Orange oil and oil soluble flavours are premixed. The active ingredients as mentioned under 1.6 are dry mixed and then stirred preferably into the fruit juice concentrate mixture (1.1).

In order to prepare the soft drink compound all parts 3.1.1 to 3.1.6 are mixed together before homogenising using a Turrax and then a high-pressure homogenizer (p_1 = 200 bar, p_2 = 50 bar).

II. A Bottling Syrup is prepared from the following ingredients:

[g]

Softdrink compound	74.50
Water	50.00
Sugar syrup 60° Brix	150.00

The ingredients of the bottling syrup are mixed together. The bottling syrup is diluted with water to 1 l of ready to drink beverage.

Variations :

Instead of using sodium benzoate, the beverage may be pasteurised. The beverage may also be carbonised.

Example 5

5 Cereal Bread

Typical serving: 50 g

Active ingredients:

EGCG and one or more additional components selected from pantethine, Coenzyme Q-10, phytanic acid and lipoic acid are incorporated in this food items

Pantethine: 20-800 mg/ per serving
EGCG: 5-500 mg/ per serving
Phytanic acid: 20-2000 mg/ per serving
Lipoic acid: 5-500 mg/ per serving
Coenzyme Q-10: 1-400 mg/ per serving

Policosanol: 0.1-20 mg/ per serving

Other components :	[%]
5 cereal flour	56.8
Water	39.8
Yeast	2.3
Salt	1.1

The yeast is dissolved in a part of the water. All ingredients are mixed together to form a dough. Salt is added at the end of the kneading time. After fermentation, the dough is

reworked and divided before a loaf is formed. Before baking, the surface of the loaf is brushed with water and sprinkled with flour.

Procedure:

Kneading:

Spiral kneading system	4 min 1st gear, 5 min 2nd gear
Dough proofing:	60 min
Dough temperature:	22 - 24 °C
Proofing time:	30 min

Baking:

Oven:	Dutch type oven
Baking temperature:	250/220 °C
Baking time:	50 - 60 min

Example 6

Cookies Type Milano

Typical serving: 30 g

Active ingredients:

EGCG and one or more additional components selected from pantethine, Coenzyme Q-10, phytanic acid and lipoic acid are incorporated in this food items

Pantethine: 20-800 mg/ per serving

EGCG: 5-500 mg/ per serving

Phytanic acid: 20-2000 mg/ per serving

Coenzyme Q-10: 1-400 mg/ per serving

Lipoic acid: 5-500 mg/ per serving

Policosanol: 0.1-20 mg/ per serving

Other components:	[g]
Wheat Flour, type 550	41.0
Sugar	20.5
Fat/Butter	20.5
Whole egg (liquid)	18.0
Lemon Flavour	q.s.

Baking agent	q.s.

All ingredients are added slowly under mixing to form a sweet short pastry.

Afterwards, the pastry is kept cool (4°C) for at least 2 hours before flattening the pastry to a thickness of approx. 5 mm. Pieces are cut out and brushed with egg yolk on the surface before baking.

Baking:

Oven:	fan oven
Baking temperature:	180 °C
Baking time:	15 min

Example 7

Toast

Typical serving: 100 g

Active ingredients:

EGCG and one or more additional components selected from pantethine, Coenzyme Q-10, phytanic acid and lipoic acid are incorporated in this food items

Pantethine: 20-800 mg/ per serving
EGCG: 5-500 mg/ per serving
Phytanic acid: 20-2000 mg/ per serving
Coenzyme Q-10: 1-400 mg / per serving
Lipoic acid: 5-500 mg/ per serving
Policosanol: 0.1-20 mg/ per serving

Other components:	[%]
Wheat Flour, type 550	55.4
Water	33.2
Yeast	2.8
Salt	1.1
Fat/Butter	5.5
Malt	0.6
Emulsifier baking agent	1.4

The yeast is dissolved in a part of the water. All ingredients are mixed together to form a dough. Salt is added at the end of the kneading time. Afterwards, the dough is reworked, divided and placed in a baking tin for fermentation. After baking, the loaf is unmoulded directly.

Procedure:

Kneading:

Spiral kneading system	5 - 6 min 1st gear; 3 - 4 min 2nd gear
Dough proofing:	none
Dough temperature:	22 - 24 °C
Proofing time:	40 min

Baking:

Oven:	Dutch type oven
Baking temperature:	220 °C
Baking time:	35 - 40 min

Example 8

Yoghurt - set type; 3.5% fat

Typical serving: 225 g

Active ingredients:

EGCG and one or more additional components selected from pantethine, EGCG, phytanic acid and lipoic acid are incorporated in this food items

Coenzyme Q-10: 1-400 mg/ per serving
Pantethine: 20-800 mg/ per serving
EGCG: 5-500 mg/ per serving
Phytanic acid: 20-2000 mg/ per serving
Lipoic acid: 5-500 mg/ per serving
Policosanol: 0.1-20 mg/ per serving

Other components:	[%]
Full fat milk (3.8% fat)	90.5
Skimmed milk powder	2.0

Sugar	5.0
Culture	2.5

The milk is heated to 35 °C before addition of milk powder, stabiliser, sugar and active ingredients. This mixture is heated to 65 °C to dissolve all ingredients. Then the mixture is homogenized in a high-pressure homogenizer (p_1 = 150 bar, p_2 = 50 bar) at 65 °C. This emulsion is then pasteurised at 80 °C for 20 minutes. After cooling to 45 °C natural yoghurt/culture is added and mixed. Then this mixture is filled into cups and fermented at 45 °C for 3-4 hours until a pH of 4.3 is reached and then stored at 4 °C.

Example 9

Yoghurt - stirred type; 3.5% fat

Typical serving: 225 g

EGCG and one or more additional components selected from pantethine, Coenzyme Q-10, phytanic acid and lipoic acid are incorporated in this food items :

Coenzyme Q-10: 1-400 mg / per serving
Pantethine: 20-800 mg/ per serving
EGCG: 5-500 mg/ per serving
Phytanic acid: 20-2000 mg/ per serving
Lipoic acid: 5-500 mg/ per serving
Policosanol: 0.1-20 mg/ per serving

Other components:	[%]
Full fat milk (3.8% fat)	90.2
Skimmed milk powder	2.0
Stabiliser	0.3
Sugar	5.0
Culture	2.5

The milk is heated to 35 °C before addition of milk powder, stabiliser, sugar and active ingredients. This mixture is heated to 65 °C to dissolve all ingredients before homogenisation in a high-pressure homogenizer (p_1 = 150 bar, p_2 = 50 bar) at 65 °C. This emulsion is then pasteurised at 80 °C for 20 minutes. After cooling to 45 °C natural yoghurt/culture is added and mixed, followed by fermentation at 45 °C for 3-4 hours until

a pH of 4.3 is reached. After cooling and stirring vigorously, the yoghurt is filled in cups and stored at 4 °C.

Example 10

Ice cream; 8% fat

Typical serving: 85 g

Active ingredients:

EGCG and one or more additional components selected from pantethine, Coenzyme Q-10, phytanic acid and lipoic acid are incorporated in this food items

Coenzyme Q-10: 1-400 mg/ per serving
Pantethine: 20-800 mg/ per serving
EGCG: 5-500 mg/ per serving
Phytanic acid: 20-2000 mg/ per serving
Lipoic acid: 5-500 mg/ per serving
Policosanol: 0.1-20 mg/ per serving

Other components:	[g]
Milk (3.7% fat)	600.00
Cream (35% fat)	166.00
Skim milk powder	49.10
Sugar	109.00
Glucose syrup 80%	70.00
Ice cream stabiliser	5.00
Flavor	q.s.
Color	q.s

Sugar, skim milk powder and stabiliser are added to the milk and cream, mixed and heated to 45 °C. Then the colour as stock solution and the glucose syrup is added as well as the active ingredients. The mix is heated up and pasteurized (20 min, 80 °C). Then a homogenization step takes place. Afterwards the mix is cooled down under constant stirring and the flavour is added at 5°C. The mix maturated at 5 °C during at least 4 h and then passed through an the ice cream machine (overrun ca. 100%). The ice cream is filled into cups and stored at -20 to -30 °C.

Example 11

Wine gums

Active ingredients:

EGCG and one or more additional components selected from pantethine, EGCG, phytanic acid and lipoic acid are incorporated in this food items

Coenzyme Q-10: 1-400 mg / per 30 g
Pantethine: 20-800 mg/ per 30 g
EGCG: 5-500 mg/ per 30 g
Phytanic acid: 20-2000 mg/ per 30 g
Lipoic acid: 5-500 mg/ per 30 g
Policosanol: 0.1-20 mg/ per serving

Other components:	[g]
Gelatine 200 Bloom	80.0
Water I	125.0
Sugar crys.	290.0
Water II	120.0
Glucose-syrup DE 38	390.0
Citric acid	10.0
Flavour	2.0
Colour	q.s.
Yield ca	1000.0

Disperse gelatine in water I, stir and dissolve by heating over a stream bath or using a microwave. Mix sugar with water II and bring to boiling until a clear solution is obtained. Remove from heat source. Mix with glucose syrup while dissolved sugar solution is still hot. Slowly add the gelatine solution. Let rest until foam on surface can be removed and 60-65°C is reached. Add flavour, citric acid and the colour solution as well as active ingredients under stirring. Deposit into moulds printed into starch trays and let sit for at least 48 hours at RT. Remove starch powder and polish with oil or wax. Dry at RT and package into airtight pouches

What is claimed is :

1. A composition for the treatment or prevention of type 2 diabetes in those individuals with pre-diabetes, or impaired glucose tolerance (IGT) or obesity comprising at least two components selected from EGCG, pantethine or a metabolite thereof, phytanic acid, lipoic acid, policosanol and coenzyme Q-10.

2. A composition for the treatment or prevention of type 2 diabetes in those individuals with pre-diabetes, or impaired glucose tolerance (IGT) or obesity comprising at least two components selected from EGCG, pantethine or a metabolite thereof, phytanic acid, lipoic acid and coenzyme Q-10.

3. A composition as in claim 1 or 2 wherein EGCG and pantethine are present.

4. A composition as in claim 1 or wherein EGCG and phytanic acid are present.

5. A composition as in claim 1 or 2 wherein pantethine and phytanic acid are present.

6. A composition as in claim 3 or 4 containing EGCG in an amount sufficient to administer to a subject a daily dosage of 0.3 mg per kg body weight to about 30 mg per kg body weight.

7. A composition as in claim 3 or 5 containing pantethine in an amount sufficient to administer to a subject a daily dosage of 1 mg per kg body weight to about 50 mg per kg body weight.

8. A composition as in claim 4 or 5 containing phytanic acid in an amount sufficient to administer to a subject a daily dosage of 1 mg per kg body weight to about 100 mg per kg body weight.

9. A composition as in any one of claims 1-8 wherein lipoic acid is present.

10. A composition as in claim 9 wherein lipoic acid is present in an amount sufficient to administer to a subject a daily dosage of 0.3 mg per kg body weight to about 30 mg per kg body weight.

11. A composition as in any one of claims 1-10 wherein coenzyme Q-10 is present.

12. A composition as in claim 11 wherein coenzyme Q-10 is present in an amount sufficient to administer to a subject a daily dosage of 0.01 mg per kg body weight to about 30 mg per kg body weight.

13. A composition as in any one of claims 1-12 wherein policosanol is present.

14. A composition as in claim 13 wherein policosanol is present in an amount sufficient to administer to a subject a daily dosage of 0.002 mg per kg body weight to about 1.5 mg per kg body weight.

15. A composition as in any one of claims 1-14 which is in dosage unit form.

16. A composition as in claim 15 wherein the dosage unit form is a solid dosage unit form.

17. A composition as in claim 16 wherein the dosage unit form contains about 10 mg to about 500 mg of EGCG.

18. A composition as in claim 16 wherein the dosage unit form contains about 20 mg to about 1000 mg of pantethine.

19. A composition as in claim 16 wherein the dosage unit form contains about 30 mg to about 500 mg of phytanic acid.

20. A composition as in any one of claims 1-14 which is a food or beverage or a supplement composition for a food or beverage.

21. A food or beverage comprising at least two components selected from EGCG, pantethine or a metabolite thereof, phytanic acid, lipoic acid, policosanol and coenzyme Q-10.

22. The use of at least two components selected from EGCG, pantethine or a metabolite thereof, phytanic acid, lipoic acid, policosanol and coenzyme Q-10 in the manufacture of a nutraceutical composition.

23. The use as in claim 22 of a combination of EGCG and pantethine, or EGCG and phytanic acid, or pantethine and phytanic acid, said EGCG being used in an amount sufficient to provide a daily dosage of 0.3 mg per kg body weight to about 30 mg per kg body weight of the subject to which it is to be administered, said pantethine being used in an amount sufficient to provide a daily dosage of 1.0 mg per kg body weight to about 50 mg per kg body weight of the subject to which it is to be administered and said phytanic acid being used in an amount sufficient to provide a daily dosage of 1.0 mg per kg body weight to about 100 mg per kg body weight of the subject to which it is to be administered

24. The use as in claim 23 wherein the nutraceutical composition is a food or beverage, or a supplement composition for food or beverage.

25. The use as in claim 23 wherein the nutraceutical composition is intended for the treatment of both type 1 and 2 diabetes, and for the prevention of type 2 diabetes in those individuals with pre-diabetes, or impaired glucose tolerance (IGT) or obesity.

26. The use as in claim 23 wherein the nutraceutical composition is a pharmaceutical composition for the treatment of both type 1 and 2 diabetes, and for the prevention of type 2 diabetes in those individuals with pre-diabetes, or impaired glucose tolerance (IGT) or obesity.

27. A method for the treatment of both type 1 and 2 diabetes, and for the prevention of type 2 diabetes in those individuals with pre-diabetes, or impaired glucose tolerance (IGT) or obesity which comprises administering to a subject in need of such treatment at least two components selected from EGCG, pantethine or a metabolite thereof, phytanic acid, lipoic acid, policosanol and coenzyme Q-10.

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(71) Applicant *(for all designated States except US)*: **DSM IP ASSETS B.V.** [NL/NL]; Het Overloon 1, NL-6411 TE Heerlen (NL).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **RAEDERSTORFF, Daniel** [FR/FR]; 36c rue Bellevue, F-68350 Brunstatt (FR). **TEIXEIRA, Sandra, Renata** [PT/CH]; Gempenstrasse 46, CH-4053 Basel (CH). **WEBER, Peter** [DE/DE]; Im Grundacker 10, 79429 Malsburg-Marzell (DE).

(74) Agent: **SCHWANDER, Kuno, Josef**; Roche Vitamins Ltd., Patent Department (VMD), Wurmisweg 576, CH-4303 Kaiseraugst (CH).

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(54) Title: NOVEL NUTRACEUTICAL COMPOSITIONS COMPRISING EPIGALLOCATECHIN GALLATE

(57) Abstract: The invention relates to nutraceutical compositions comprising at least two ingredients from the groups of EGCG, pantethine or a metabolite thereof, phytanic acid, lipoic acid, policosanol and coenzyme Q-10 and their use in the treatment or prevention of diabetes or obesity.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/10838

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/353 A61K31/16 A61K31/20 A61K31/385 A61K31/575
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, WPI Data, PAJ, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 976 568 A (RILEY PATRICIA A) 2 November 1999 (1999-11-02) column 6, line 63 - column 7, line 1; table II	1-27
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-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 May 2004	01/06/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zimmer, B

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 02/072086 A (CONSORZIO PER GLI STUDI UNI ;SUZUKI HISANORI (IT)) 19 September 2002 (2002-09-19) claim 3	1-27
Y	EP 1 177 789 A (ROCHE VITAMINS AG) 6 February 2002 (2002-02-06) claim 1	1-27
Y	RETT K ET AL: "'Lipoic acid acutely ameliorates insulin sensitivity in obese subjects with type 2 diabetes!. ALPHA-LIPONSAURE (THIOCTSAURE) STEIGERT DIE INSULINEMPFINDLICHKEIT UBERGEWICHTIGER PATIENTEN MIT TYP-II-DIABETES" DIABETES AND STOFFWECHSEL, KIRCHHEIM, DE, vol. 5, no. SUPPL 3, 1996, pages 59-63, XP002113908 ISSN: 0942-0037 abstract	1-27
Y	MCCARTY M F: "TOWARD PRACTICAL PREVENTION OF TYPE 2 DIABETES" MEDICAL HYPOTHESES, EDEN PRESS, PENRITH, US, vol. 54, no. 5, May 2000 (2000-05), pages 786-793, XP001019681 ISSN: 0306-9877 page Y	1-27
Y	MCCARTY M F: "Hepatothermic therapy of obesity: Rationale and an inventory of resources" MEDICAL HYPOTHESES 2001 UNITED KINGDOM, vol. 57, no. 3, 2001, pages 324-336, XP009030758 ISSN: 0306-9877 p. 331, left col., last paragraph abstract	1-27
E	WO 2004/017766 A (EGGERSDORFER MANFRED LUDWIG ;TEIXEIRA SANDRA RENATA (CH); WEBER PE) 4 March 2004 (2004-03-04) the whole document	1-27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/10838

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy Although claim 27 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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